REMARKS

The Claim Amendments

Claims 1, 8-10, and 26-30 are pending. Claims 2-7 and 11-25 were previously canceled as drawn to a non-elected invention. Claim 8 has been canceled without prejudice in this amendment. New claims 27-30 have been added. Claim 1 has been amended to recite a method of identifying a beta-catenin inhibitory agent using an assay system comprising a UP nucleic acid, contacting the assay system with a test agent and detecting reduced expression of UP nucleic acid. Support for the amendment is found throughout the specification and in particular at, for example, pages 34-41.

Claims 13, 14, and 26 have been amended merely correct their dependencies and to provide proper antecedent basis.

New claim 27 recites "[t]he method of Claim 1, wherein the assay system comprises cultured cells that express UP." Support for the amendment is found throughout the specification.

New claim 28 recited "[t]he method of claim 27, wherein the cultured cells additionally have increased beta catenin function." Support for the amendment is found throughout the specification.

New claim 30 recites "[t]he method of Claim 1, comprising the additional steps of:
(d) providing a second assay system capable of detecting an inhibition in the beta catenin pathway comprising cultured cells expressing UP; (e) contacting the assay system of step (d) with the test agent of step (b); (f) measuring the beta catenin pathway in the presence or absence of the test agent; and (g) confirming that the test agent of step (b) is a beta catenin inhibitory agent by detecting an inhibition in the beta catenin pathway in the presence or absence of the test agent." Support for the amendment is found throughout the specification and in particular at, for example, pages 34-41.

The claim amendments are made solely in an effort to advance prosecution and are made without prejudice, without intent to acquiesce in any rejection of

record, and without intent to abandon any previously claimed subject matter. No new matter has been added by way of these amendments.

Claim Objections

The Office objected to claim 8 under 37 CFR 1.75(c), as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim (claim 1). Claim 8 has been canceled, rendering the objection moot. Accordingly, Applicants respectfully request withdrawal of the claim objection.

Claim 10 was objected to because for allegedly having improper dependency. Claim 10 has been amended to depend from claim 9, thereby obviating the objection.

35 U.S.C. § 103(a) Rejections

Claims 1, 8-10, and 26 were rejected under 35 USC § 103(a) as allegedly being unpatentable over Deenen et al. (Cancer Research, 63: 4268-4274 (2003)) in view of Monga et al (Gastroenterology 124:201-216 (2003)) and Verma et al. (Clinical Cancer research, 9:1291-1300 (2003)). Applicants respectfully traverse the rejections.

The Office Action stated that Deneen et al. suggest that uridine phosphorylase contributes to pathways that initiate cellular proliferation and that uridine phosphorylase promotes cellular transformation by impacting other physiological mechanisms directly linked to cellular proliferation or survival. Office Action, page 4. The Office admitted that Deneen et al. do not teach identifying a "candidate" beta-catenin pathway modulating agent based on the changed expression level of uridine phosphorylase. The Office Action further stated that Monga et al. and Verma et al. teach that the Wnt signaling pathway involving beta-catenin regulates cellular proliferation and that an antisense PMO (Monga et al.) and an siRNA (Verma et al.) targeted to beta-catenin decreases

cellular proliferation compared with appropriate controls.

The Office concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to make an antisense PMO or an siRNA against uridine phosphorylase, wherein the antisense PMO or siRNA functions as a "candidate" agent that is likely to inhibit cellular proliferative activity mediated by beta-catenin in the Wnt/beta-catenin signaling pathway. The Office argued that since Monga et al and Verma et al teach that antisense and siRNA against beta-catenin are useful to inhibit cell proliferation (ie, teach an "art-recognized goal"), it would have been apparent to one of ordinary skill in the art to identify other "candidate" antisense PMO or siRNA compounds. Although not stated directly, the Office indicated that uridine phosphorylase (UP) was an obvious gene target because Deenen et al. suggests that UP participates in and contributes to the beta-catenin-mediated cell proliferation pathway (see Deneen et al.), and therefore antisense and siRNA against UP are "likely" to inhibit beta-catenin activity (e.g., cell proliferation). The Office further stated that one of ordinary skill in the art would have had a reasonable expectation of success in identifying an antisense PM0 or siRNA targeted to uridine phosphorylase as a "likely" or "suitable" candidate beta-catenin pathway modulating agent since the likelihood of the functional role of uridine phosphorylase in participating in or influencing the Wnt/beta-catenin signaling pathway for promoting cellular proliferation was reasonably, if not absolutely, established in the art as suggested by Deneen et al., and since the utility of antisense PMOs and siRNAs for inhibiting target-specific gene expression/activity in a cell, especially for inhibiting beta-catenin activity, was known in the art as taught by Monga et al. and Verma et al.

Contrary to the Office's allegations, the teachings of Deneen et al, Monga et al., and Varga et al, alone or in combination, do not render obvious the present invention. The instant claims are directed to a method of identifying a beta-catenin pathway inhibitory agent comprising the steps of: (a) providing an assay system comprising a UP nucleic acid; (b) contacting the assay system with a test agent; and (c) detecting reduced expression of UP in the presence of the test agent

compared to the absence of the test agent. Thus, the present claims utilize an assay system for detecting reduced expression of UP nucleic acid to identify a beta-catenin pathway inhibitory agent.

Neither Deneen et al, Monga et al, nor Varga et al. teach the connection between UP expression and the beta-catenin pathway. Thus, contrary to the Office's allegation, the cited references, alone or in combination, fail to suggest that UP participates in the Wnt/beta-catenin signaling pathway and certainly fail to provide a reasonable expectation that an antisense PMO or siRNA targeted to uridine phosphorylase would successfully function as a beta-caten ininhibitory agent.

The Office is incorrect in its statement that Deneen et al. suggests that uridine phosphorylase participates in and contributes to the beta-catenin-mediated cell proliferation pathway. Deneen et al. provides no teaching or suggestion whatsoever that UP participates in the Wnt/beta-catenin signaling pathway. Deneen et al. is concerned only with the study of EWS/ETS-mediated transformation. With this focus, the teaching in Deneen et al. is limited to studying factors that contribute to EFT (Ewings Family Tumor) oncogenesis. Contrary to the Office's contention, Deneen et al. fails to provide a broader teaching relating to general cell proliferation and, in the absence of any mention whatsoever of the Wnt/beta-catenin signaling pathway, certainly fails to provide any specific teaching relating to factors involved in the beta-catenin pathway.

Deneen et al teaches that: (1) EWS/ETS fusion proteins play a role in cellular transformation and are required for the growth of EFT (Ewings Family Tumor) cell lines; (2) EWS/ETS fusion proteins up-regulate the expression of UP; (3) activation of RAS up-regulates the expression of UP; (4) UP may play a role in the oncogenesis of EFT cells or cells that express EWS/ETS fusion protein. Contrary to the Office's contention, Deneen et al does not teach or suggest a general role for UP in cell proliferation or a role for UP in the beta-catenin pathway. The fact that UP is up-regulated by EWS/ETS fusion proteins in EFT tumor cells does not amount to a suggestion that it is involved in modulating the beta-catenin pathway.

The Office refers to page 4273, right column, of Deneen et al, stating that "Deneen et al. suggest that 'uridine phosphorylase contributes to pathways that initiate cellular proliferation' and that 'uridine phosphorylase is promoting cellular transformation by impacting other physiological mechanisms directly linked to cellular proliferation or survival'. However, a fair and proper reading of page 4273, right column, actually reveals that Deneen et al. has no idea how UP functions in cell proliferation and merely presents several different hypotheses with no data to support any of them. The following statements make clear that Deneen et al is merely hypothesizing on a possible role for UP in cell proliferation, angiogenic functions, and cell survival, and that further study is required to determine the function of UP in these pathways:

(1) "It may be that uridine phosphorylase contributes to pathways that initiate cellular proliferation and not to pathways required for tumor induction or maintenance."

(2) "That the enzymatic activities of thymidine phosphorylase and uridine phosphorylase are similar could result in similar angiogenic functions between these proteins."

(3) "It may be that the association of pyrimidine nucleoside phosphorylase activity with angiogenesis is analogous to the association of polyamine biosynthesis with cell survival."

(4) Another possibility is that uridine phosphorylase is promoting cellular transformation by impacting other physiological mechanisms directly linked to cellular proliferation or survival."

(5) "Additional examination of the impact of uridine phosphorylase overexpression on global cellular metabolism may prove insightful in delineating these relationships."

Notably, Deneen et al fails to even mention a role for UP in the Wnt/beta-catenin pathway in any of its various hypotheses.

The Office appears to allege that a teaching that UP is involved in the oncogenesis of a specific tumor amounts to a teaching that UP is involved in general cell proliferation and indeed has a role in the Wnt/beta-catenin pathway.

However, as one of ordinary skill in the art well knows, the wnt/beta-catenin pathway is only one of dozens of different pathways involved in cell proliferation. In the absence of any teaching whatsoever in Deneen et al relating to cell proliferation pathways, one of ordinary skill in the art would have no way of knowing in which of these numerous different cell proliferation pathways UP plays a role and would not have surmised that UP had a role in the Wnt/beta-catenin pathway absent a discussion of this pathway.

Monga et al. and Verma et al fail to cure the deficiencies of Deneen et al. The teachings in Monga et al. and Verma et al are limited to antisense and siRNA targeted to beta-catenin. Neither Monga et al, nor Verma et al. even mentions UP, much less teaches or suggests a connection between UP and the beta-catenin pathway. The fact is that, prior to Applicants' disclosure, there was no reported nexus between beta-catenin and UP and no indication whatsoever that UP was involved in the regulation of the beta-catenin pathway. In the absence of any teaching or suggestion whatsoever in any of the references of a connection between UP and beta-catenin, the references, alone or in combination fail to teach an assay system for detecting reduced expression of UP nucleic acid to identify a beta-catenin pathway inhibitory agent.

The Office states that "it would have been apparent to one of ordinary skill in the art that identifying other 'candidate' antisense PMO or siRNA compounds such as those targeted to uridine phosphorylase that was suggested to participate in and contribute to the beta-catenin-mediated cell proliferation pathway (see Deneen et al.), wherein such compounds are 'likely' to inhibit beta-catenin activity (e.g., cell proliferation) would have appeared useful for inhibiting beta-catenin-mediated cell proliferative activity." Office Action, pages 5-6. In other words, the Office argued that, in view of the teachings of Monga et al and Verma et al., one of ordinary skill in the art to would have been motivated to seek other 'candidate' antisense PMO or siRNA compounds that inhibit beta-catenin and would have selected UP based on the teachings of Deneen et al.

However, Applicants submit that one skilled in the art would not have been motivated to combine the teachings of Deneen et al. with Monga et al and/or Verma et al. based on the "art-recognized goal" of seeking beta-catenin modulators. Neither Monga et al, nor Verma et al. even mention UP, much less suggest that UP is a possible beta-catenin modulator. Furthermore, for the reasons previously discussed, the functional role of uridine phosphorylase in participating in or influencing the Wnt/beta-catenin signaling pathway was not reasonably established by the teachings of Deneen et al. There was simply no teaching or suggestion of connection between UP and the Wnt/beta-catenin pathway in any of the cited references. Absent a teaching or suggestion of UP involvement in the beta-catenin pathway, one of ordinary skill in the art would not have been motivated to combine the teachings of Deneen et al., Monga et al., and Verma et al.. Applicants submit that the Office has engaged in impermissible hindsight reasoning. The Office is using the benefit of Applicants' own disclosure to conclude that one skilled in the art would have known to test a UP inhibitor as a beta-catenin inhibitor agent.

Further, even if for the sake of argument, one skilled in the art were motivated to combine the teachings of the cited references, the requirements for obviousness are still not met because the combined teachings do not teach or suggest all of the limitations of the claimed invention. To meet the requirements for *prima facie* case of obviousness, the Office must demonstrate that the references, alone or in combination, teach or suggest all the limitations of the claims. Specifically, the Patent Office maintains that:

> [A]n examiner must make "a searching comparison of the claimed invention — including all its limitations - with the teaching of the prior art." In re Ochiai, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." CFMT, Inc. v. *Yieldup Intern.* Corp., 349 F.3d, 1333, 1342 (Fed. Cir. 2003) (citing In *re Royka,* 490 F.2d 981, 985 (CCPA 1974)). Ex *Parte Wada,* BPAI, Appeal 2007-377, page 7 (Jan. 15, 2008) (unpublished). *See also, Ex parte Shepard,* BPAI, Appeal 2008-0401, page 7 (Jan. 3, 2008)(unpublished).

For the reasons previously discussed, the teachings of Deneen et al, Monga et al, and Verma et al fail to teach the nexus between UP and the beta-catenin pathway. Furthermore, none of the references even mention screening assays, much less suggest using a screening assay for the purpose of identifying beta-catenin pathway inhibitory agents. The instant method requires: (a) providing an assay system comprising a uridine phosphorylase (UP) nucleic acid; (b) contacting the assay system with a test agent; and (c) detecting reduced expression of UP nucleic acid in the presence of the test agent compared to the expression in the absence of said test agent to identify the test agent as a beta-catenin pathway inhibitory agent. Deneen et al fails to mention the beta-catenin pathway, much less suggest a method for identifying beta-catenin pathway inhibitory agents. Likewise, Monga et al and Verma et al. fail to contemplate use of a screening assay to identify beta-catenin pathway inhibitory agents. Further, none of the references teach or suggest a nexus between UP and the beta-catenin pathway and therefore fail to suggest a screening assay that detects reduced expression of UP to identify a beta-catenin pathway inhibitory agent. The cited references alone or in combination fail to teach the elements of the claimed methods.

Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness based on the teachings of Deneen et al, Monga et al, and Verma et al. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection of claims 1, 8-10, and 26.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the Examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

Date: August 16, 2010

/Sherri L. Oslick/

Sherri L. Oslick, Ph.D.
Registration No. 52,087

McDonnell Boehnen Hulbert & Berghoff LLP
300 S. Wacker Drive, Ste. 3100
Chicago, IL 60606
Phone: 312-913-0001
Fax: 312-913-0002